REMARKS/ARGUMENTS

With entry of this amendment, claims 1-6, 8-19, 21-23, 25-29, and 40-48 are pending in the above-identified application. Claims 10-12, 14, 23, 27, 44, and 45 have been withdrawn by the Examiner as drawn to a non-elected invention. Claims 30-39 were previously canceled. By this amendment, claims 7, 20, 21, and 24 are canceled; claims 1, 22, 25, 40, and 43 are amended; and claims 46-48 are added as set forth in detail below. Support for these amendments is identified in the following remarks. No new matter has been added by these amendments. Applicants reserve the right to pursue claims of original scope, including any canceled claims, in a related, co-pending application. Examination and reconsideration of all pending claims are respectfully requested.

Claim Objections

The Examiner has objected to claim 43 because the therapeutic agent Trazodone, as written in the specification, was spelled "Trazedone." Applicant has amended claim 43 to recite "Trazodone." Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2, 21, and 29 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner contends that the phrases "an undesired side effect" and "a side effect" are vague and indefinite "because the specification recites any number of undesired side effects." With respect to claim 21, this rejection is obviated in view of the cancellation of this claim. As to claims 2 and 29, Applicant traverse the rejection.

According to the MPEP and the Federal Circuit, a claim is definite where one of skill in the art would understand the scope of the claim when read in light of the specification.[1] Thus, a term is generally definite where the meaning of a claim term is apparent from the

specification or the prior art, provided that there is no inconsistency with the specification or prior art in the manner in which the claim term is used.[2] Further, breadth of a claim is not to be equated with indefiniteness.[3]

In the present case, the term "side effect" has a well-established meaning in the pertinent art. As evidenced by *Stedman's Medical Dictionary* (27th ed. 2000) (Exhibit 1, attached hereto), the term "side effect" is well-understood to mean a result of a drug or other therapy "in addition to or in extension of the desired therapeutic effect," typically, although not necessarily, an undesirable effect.[4] This meaning is consistent with the use of the terms "side effect" and "undesirable side effect" in claims 2 and 29, as well as with the use of these terms in the specification.[5] Furthermore, the fact that the term is broad so as to include "any number of side effects" is inapposite, as breadth of a term should not be equated with indefiniteness. A skilled artisan would understand, in the context of a particular therapeutic regimen, whether any given effect of an agent is a "side effect" or "undesirable side effect," and thus whether the this claim limitation is met.

In view of the above, Applicant believes claims 2 and 29 to be definite under 35 U.S.C. § 112, second paragraph. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-9, 13, 15-22, 24-26, 28, 29, and 40-43 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the full scope of the these claims, in particular, the full scope autoimmune conditions (claims 1-9, 13, 15-22, 24-26, 28, and 29); sleep restorative agents (claims 1-8, 13, 15-22, 24-26, 28, 29, and 40-42); and therapeutic agents

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[1] *See, e.g.*, MPEP §§ 2171 and 2173.02. *See also North Am. Vaccine, Inc. v. American Cyanamid Co.*, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993).
[2] *See, e.g.*, MPEP §§ 2173.03 and 2173.05(a).
[3] *Id.* at § 2173.04.
[4] *Stedman's Medical Dictionary* (Lippincott Williams & Wilkins, 27th ed. 2000), at p. 1634 (Exhibit 1).
[5] *See* specification at page 19, line 27, to page 20, line 15

(claims 1-9, 13, 15-22, 24-26, 28, 29, 40, 41, and 43). This rejection is overcome in part and traversed in part as set forth below.

First, while not agreeing with the rejection or reasons for rejection, but to expedite prosecution of the instant application, independent claims 1, 25, and 40 have been amended to recite that the sleep restorative agent "reduces excessive sympathetic tone of the subject." Support for this amendment is found in the application as filed at, for example, page 3, lines 7 and 8; page 5, lines 16-21; page 23, line 7 to page 24, line 17; and original claim 7. In view of this amendment, original claim 7 has been canceled to eliminate redundancy in the claims. For reasons set forth further herein, in view of the knowledge in the art as of the effective filing date, the skilled artisan would readily accept the presently claimed invention as enabled by Applicant's disclosure, particularly in light of Applicant's demonstration, in an extensive number of working examples, showing that the method is effective for a wide range of autoimmune diseases, therapeutic agents, and sleep restorative agents that reduce sympathetic tone.

In setting forth the present rejection, the Examiner references the following factors enumerated by the Federal Circuit in *In re Wands*[6]:

(1) the nature of the invention;

(2) the breadth of the claims

(3) the state of the prior art;

(4) the predictability in the art;

(5) the guidance in the specification;

(6) working examples; and

(7) the quantity of experimentation necessary.

Applicant will also address each of the above factors in turn.

[6] 8 USPQ2d 1400 (Fed. Cir. 1988).

The Nature of the Invention

The claims as presently amended recite that the sleep restorative agent reduces sympathetic tone in the subject having an autoimmune condition. Accordingly, the nature of the invention pertains in part to sympathetic control of the immune system for treatment of autoimmune disease.

With particular regard to the nature of the disease treated, Applicant notes that, while the etiology of different autoimmune diseases may vary, it was well-known that the pathology of all autoimmune diseases share certain mechanistic similarities, including migration of self-reactive lymphocytes into involved tissue. As evidence of this knowledge in the art, Applicants have attached hereto Exhibit 2 (Rose, Abstract),[7] which refers to the penetration of tissue spaces and cellular attack by T cells as a principal mechanism of autoimmune pathology.

Further, as of the effective filing date of the instant application, it was known in the art that an interface exists between the sympathetic nervous system and the immune system. As evidence of this knowledge in the art, Applicants refer the Examiner to Exhibit 3 (attached, also referred to herein as "Elenkov *et al.*"[8]). In particular, Elenkov *et al.* states that the sympathetic nervous system plays a significant role in, for example, control of lymphocyte traffic and circulation.[9]

What was not known as of the filing date, however, was whether modulation of sympathetic tone, via administration of sleep restorative agents, could be utilized in the treatment of autoimmune disease by increasing the efficacy of a therapeutic agent for treatment of the disease, and thereby decreasing the effective amount of a therapeutic agent needed for such treatment. This inventive insight is provided by Applicant's disclosure, including through the demonstration of increased efficacy of a wide range of therapeutic agents for the treatment of a wide range of different autoimmune diseases using a wide range of different sleep restorative agents known to decrease sympathetic tone. The specification further presents an explanation for

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[7] Rose, *Clin. Immunol. Immunopathol.* 53:S7-16, 1989 (Abstract) (Exhibit 2).
[8] Elenkov *et al.*, *Pharmacol. Rev.* 52:595-638, 2000 (Exhibit 3).
[9] *See id.* at p. 612, second col., to p. 613, first col.

how reduction in sympathetic tone can act to increase efficacy of therapeutic agents, irrespective of the particular disease or agent – through, *inter alia*, a decrease in capillary porosity with a concomitant decrease in access of lymphocytes to involved tissue.[10]

In light of the above, Applicant disagrees with the Examiner's contention that the variety of autoimmune diseases and agents encompassed by the claims renders the nature of the invention "complex." While a wide variety of diseases and agents are encompassed, Applicant's invention as presently claimed includes a unifying approach for treatment generally applicable to all autoimmune disease, *inter alia*, decreasing sympathetic tone in a subject.

The Breadth of the Claims

The Examiner contends that the breadth of the claims is "greatly exacerbated by the breadth of the claims." In particular, the Examiner asserts that there are "multiple possible combinations" of "structurally distinct" sleep restorative agents and "structurally distinct" therapeutic agents for the treatment of "numerous types of autoimmune conditions."[11]

In response, Applicant emphasizes that, because the present invention is based in part on the discovery that reducing sympathetic tone will increase efficacy of therapeutic agents for treatment of autoimmune disease, the particular structure of the various sleep restorative agents is not critical, so long as the sleep restorative agent reduces sympathetic tone of the subject. The claims as amended explicitly exclude agents that do not reduce sympathetic tone.

Further, in view of the specification's teachings, the particular structure of the therapeutic agent is also not critical. The studies described in the specification show that the present invention works for any of a variety of structurally unrelated therapeutic agents, including steroids, methotrexate, azathioprine, sulfasazine, hydrochloroquine, NSAIDs, colchicine, and anti-TNFα mAb. As described in the specification, one theory for an underlying mechanism of the present invention is that reducing sympathetic tone in the subject decreases

[10] *See* Specification at p. 24, ll. 1-11.
[11] Office Action dated May 20, 2005, at pp. 5 & 6.

capillary porosity, with a concomitant decrease in the access of lymphocytes to involved tissue.[12] With decreased lymphocyte migration into diseased tissue, there is decreased need, *e.g.*, for therapeutic agents that inhibit lymphocyte function.[13]

State of the Prior Art

With respect to the state of the art, the Examiner states that while "it is known that some drugs are useful for treating multiple autoimmune diseases, other drugs are not as versatile."[14] The Examiner asserts that Christodoulos *et al.* teaches "that minocycline can be used to treat rheumatoid arthritis, but can also lead to drug-induced lupus."[15]

According to the MPEP, enablement under 35 U.S.C. § 112 is determined with respect to the level of skill in the art in relation to the pertinent subject matter.[16] Thus, a specification is enabling if it enables persons skilled in the pertinent art to carry out the aspects of the invention applicable to their specialty.[17]

Here, the pertinent art includes treatment of autoimmune disease. As of the effective filing date of the application, and as evidenced by the studies described in the specification,[18] a wide variety of therapeutic agents were being used and advanced in the clinic for treating autoimmune disease. Thus, the present invention is carried out in the context of therapeutic agents for which some efficacy in treating a particular autoimmne disease has already been shown.

Consequently, in any given case, the person of skill carrying out administration of the therapeutic agent is the clinician knowledgeable and skilled in the treatment of the particular autoimmune disease. As such, the skilled person carrying out the invention would be

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[12] *See* Specification at p. 24, ll. 1-11.
[13] *See id.*
[14] Office Action dated May 20, 2005, at p. 6; *see also* pp. 10 & 15.
[15] *Id.* at p. 6, citing Christodoulos *et al.*, *Chest.* 115:1471-1473, 1999.
[16] *See, e.g.*, MPEP § 2164.05(b).
[17] *Id.* (citing *In re Naquin*, 398 F.2d 863, 866, 158 USPQ 317, 319 (CCPA 1968)).
[18] *See* Specification at pp. 24-34.

knowledgeable as to particular therapeutic agents for which the particular autoimmune disease is indicated, as well as to potential side effects and contraindications for the therapeutic agents. For example, the clinician knowledgeable and skilled in the treatment of lupus would not consider minocycline for treatment of lupus, given the fact that this drug is not indicated for lupus and its known potential for inducing the disease. Accordingly, Applicant submits that Christodoulos *et al.* is not prejudicial to enablement of the present claims.

The Predictability in the Art

With respect to predictability in the art, Applicants also disagree with the Examiner's reliance on the statement that "physiological activity is generally considered to be an unpredictable factor."[19] As indicated above, the present invention is carried out in the context of therapeutic agents for which some efficacy in treatment of an autoimmune has been shown. Further, the Examiner's broad generalization regarding predictability of physiological activity does not take into account the specification's teachings, nor other knowledge in the art. The studies described in the specification were carried out with a wide variety of agents in different autoimmune diseases. In each case, administration of a sleep restorative agent that reduces sympathetic tone increased efficacy of the respective therapeutic agent,[20] thus indicating that the claimed method predictably works in the context of a wide range of treatments for autoimmune disease.

Still further, the specification points to an underlying mechanism for the present invention, *inter alia*, the reduction of sympathetic tone in the subject. In this respect, it is noted that the specification provides data showing that RA patients with higher sympathetic tone require more medication in addition to ENBREL® than patients with lower sympathetic tone.[21] This data directly supports that specification's teaching that lowering sympathetic tone in a subject with autoimmune disease can effect a decrease in the effective amount of a therapeutic

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[19] Office Action dated May 20, 2005, at p. 6.
[20] *See generally* Specifcation at pp. 24-34.
[21] *See id.* at p. 33, l. 11, to p. 34, l. 14.

agent for treating the disease.[22] In view of these teachings in the specification, in addition to the specification's demonstration of operability in treating different diseases and particularly in conjunction with the known interface between the sympathetic nervous system and the immune system,[23] the skilled artisan would regard the scope of the claimed method as reasonably supported by predictable factors in the art.

The Guidance in the Specification

The Examiner contends that the guidance given by the specification as to how to treat autoimmune diseases "in general is limited."[24] The only reason provided by the Examiner in this regard is the statement that the specification is directed "toward the treatment of specific autoimmune diseases such as rheumatoid arthritis and Psoriatic arthritis by administering prednisone or methotrexate concomitantly with a sleep restorative agent," and that the specification "does not give guidance for the treatment of Hashimoto's thyroiditis, for example."[25] Applicant's note that the Examiner appears to refer only to the working examples in assessing the guidance provided by the specification.

According to the MPEP and the Federal Circuit, "[h]ow a teaching is set forth, by specific example or broad terminology, is not important."[26] Also, the specification need not disclose, and preferably omits, that which is already known.[27] In the present case, as set forth further below, in view of the knowledge and skill in the pertinent art, the guidance provided in the specification is sufficient to guide the skilled artisan in carrying out the claimed invention without undue experimentation.

First, going beyond the extensive working examples provided by Applicant, the specification teaches that a sleep restorative agent that reduces sympathetic tone can be co-

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[22] *See id.* at p. 34, ll. 12-14.
[23] *See generally, e.g.*, Exhibit 3.
[24] Office Action dated May 20, 2005, at p. 6; *see also* pp. 11 & 16.
[25] *Id.* at p. 6; *see also* pp. 11 & 16.
[26] MPEP § 2164.08 (citing *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 370 (CCPA 1971)).
[27] MPEP § 2164.05(a) (citing cases).

administered with a therapeutic agent for treating autoimmune disease to decrease the effective amount of the therapeutic agent normally required in treating that disease.[28] According the specification, the sleep restorative agent can be administered according to an effective mode of administration for that agent.[29] Similarly, again as described in the specification, the therapeutic agent is administered "according to any clinically effective mode of administration, as will be appreciated by the skilled artisan."[30] The specification also points to various examples of agents, including known sleep restorative and therapeutic agents, as well as known dosage forms for administering agents.[31] Moreover, as previously noted, the specification points to reduction of sympathetic tone as an underlying mechanism for increasing efficacy of the therapeutic agent,[32] and points to known methods for assessing sleep quality as well as sympathetic tone in a subject.[33] The specification further describes monitoring the subject while therapeutic agent and sleep restorative agent are administered, and states that as efficacy of the therapeutic agent increases, the amount of the therapeutic agent required to be administered to the subject is typically decreased.[34] These teachings in the specification are then supported by an array of working examples, setting forth various studies showing, in each case, that the described method works to increase efficacy of therapeutic agents for treating autoimmune disease. These working examples demonstrate the operability of the present invention across a wide range of structurally distinct agents and different autoimmune diseases. It is submitted that this disclosure provided in the specification is sufficient to guide the skilled artisan in carrying out the invention as claimed for increasing efficacy of therapeutic agents, using sleep restorative agents that reduce sympathetic tone, in treatment of autoimmune diseases in addition to those shown to actually work in the specification, particularly in view of the knowledge in the art as previously discussed.

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[28] *See* Specification at, *e.g.*, p. 5, ll.13-24; and pp. 17-24.
[29] *See id.* at, *e.g.*, p 17, lines 10-19.
[30] *Id.* at p. 17, ll. 7-9.
[31] *See id.* at, *e.g.*, pp. 5-19.
[32] *See id.* at, *e.g.*, p. 23, l. 7, to p. 8. l. 11.
[33] *See id.* at p. 21, ll. 3-32; and p. 23, ll. 7-26.
[34] *See id.* at p. 20, ll. 16-28.

Working Examples

With respect to working examples, the Examiner refers to the *in vivo* examples of the treatment of rheumatoid arthritis and Psoriatic arthritis by administering combinations of specific therapeutic agents and sleep restorative agents. The Examiner then states, without further reasoning or evidence, that "there is a lack of working examples to bolster the generic claims." Applicant disagrees.

According to the MPEP, for a claimed genus, representative examples, together with a statement applicable to the genus as a whole, "will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation."[35] In the present case, the representative working examples provided by Applicant demonstrate treatment of a wide range of autoimmune diseases, including rheumatoid arthritis, Psoriatic arthritis, Sjogren's Syndrome, Behcet's Syndrome, Ankylosing Spondylitis, Systemic Lupus Erythematosis, ocular and articular Sarcoidosis, Palindromic Rheumatism, Reiter's Syndrome, chronic gout, pseudogout, and Multiple Sclerosis. These treatments included administration of structurally distinct sleep restorative agents, including Trazodone, Lorazepam, Clonazepam, Carisprodol, and Pramipexole; along with administration of structurally distinct therapeutic agents, including steroids, methotrexate, azathioprine, sulfasazine, hydrochloroquine, NSAIDs, colchicine, and anti-TNFα mAb. These described treatments were according to known, effective modes of administration for each agent, with resulting increases in efficacy of the therapeutic agents and, therefore, concomitant decreases in the amount of therapeutic agent needed for treatment of the respective autoimmune disease, relative to an amount needed in the absence of the sleep restorative agent.

The Examiner has provided no evidence as to why the skilled artisan would not view these working examples as representative of the claimed genus, particularly in view of the aforementioned knowledge in the art and the teachings provided in the specification. The method is shown in the specification to be operable across a wide range of diseases and agents,

without need for extensive trial and error as to effective combinations of sleep restorative agent and therapeutic agent. Accordingly, it is submitted that the skilled artisan would expect the claimed genus could be used in the manner described without undue experimentation.

The Quantity of Experimentation Necessary

With regard to quantity of experimentation, the Examiner asserts that "one of skill in the art would have to first envision a combination of an autoimmune condition, therapeutic agent, and sleep restorative agent," and would then have to test the combination in a model system. The Examiner goes on to state that the tested combination would "likely" be unsuccessful, and that the skilled artisan would essentially have to go through a reiterative process of trial and error of the "unpredictable process" until successful. Applicant disagrees with the Examiner's reliance on these statements.

First, for reasons set forth previously, the present invention is based on certain predictable factors in view of the teachings in the specification and the knowledge in the art, *inter alia*, the interface between the sympathetic nervous system and the immune system, as well as common pathological features of autoimmune disease. Further, again as previously noted, the present invention is against the backdrop of the state of art with regard to the use of various therapeutic agents in the treatment of autoimmune disease, as well as knowledge in the art with regard to use of sleep restorative agents.

In view of the teachings in the specification, the skilled artisan carrying out the invention as presently claimed would not view the particular sleep restorative agent as critical, so long as the agent reduces sympathetic tone. Further, as previously discussed, the skilled artisan with respect to administration of the therapeutic agent is the clinician skilled in the treatment of the particular autoimmune disease and, therefore, knowledgeable as to particular therapeutic agents effective for such treatment. Thus, "envisioning" a proper combination of sleep

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[35] MPEP § 2164.03.

restorative agent and therapeutic agent for treating an autoimmune disease would require undue effort on the part of the skilled artisan carrying out the method.

Moreover, Applicant notes that the test for whether experimentation is "undue" is not merely quantitative, "since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."[36] Here, for substantially the reasons set forth above, the specification provides sufficient guidance to the skilled artisan, trained in the art of treating any particular autoimmune disease, as to which direction to proceed in establishing effective combinations of sleep restorative agent and therapeutic agent. More importantly, given the many working examples set forth in the specification, Applicant submits that combinations of sleep restorative agent and therapeutic agent, selected by the skilled artisan for treating any particular autoimmune disease according to the teachings provided in the specification and the knowledge in the art, would likely be successful, contrary to the Examiner's assertion.

Claim 13 and Functional Language

With particular regard to claim 13, Applicants disagree with the Examiner's contention that this claim is not enabled due to use of "functional language to define the claim." The Examiner cites to *General Electric Company v. Wabash Appliance Corporation*[37] for the proposition that functional language is improper when such language is used "at the exact point of novelty." Applicant notes, however, that the point of novelty of the present invention does not lie with any particular immunosuppressive antibody used, nor the structure of any other therapeutic agent, for that matter. The point of novely of Applicant's invention as presently claimed is in, *inter alia*, the use of a sleep restorative agent that reduces sympathetic tone to decrease the effective amount of therapeutic agent needed to treat autoimmune disease.

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[36] MPEP § 2164.06.
[37] 37 USPQ 466, 469 (US 1938).

Accordingly, the use of functional language to describe an antibody as the therapeutic agent is proper in this case.

For at least the reasons set forth above, Applicant believe the present claims to be enabled by the specification as filed under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1-9, 13, 15-22, 24-26, 28, 29, and 40-43 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Lapin (U.S. 4,743,596) in view of Wojtulewski *et al.* (*Curr. Med. Res. Opin.* 8:456-460, 1983) and Lagos *et al.* (*Eur. Neuropsychopharmacol.* 8:113-120, 1998; referred to the Office Action as "Monti *et al.*") The Examiner asserts that Lapin teaches treatment of rheumatoid arthritis with prednisone and that Wojtulewski teaches that insomnia is a secondary condition of rheumatoid arthritis. The Examiner further states that Lagos teaches treatment of sleep disorders by administration of pramipexole. On this basis, the Examiner contends that one of skill in the art would have been motivated to use pramipexole concomitantly with prednisone to treat rheumatoid arthritis, and that such treatment would be reasonably expected to have "at least an additive effect, since both prednisone and pramipexole are known to be useful to treat rheumatoid arthritis separately." This rejection is overcome in part and traversed in part as set forth below.

First, while not agreeing with the rejection or reasons for rejection, but to expedite prosecution of the instant application, claim 1 has been amended to specify that the effective amount of the therapeutic agent "administered to the subject is decreased, as compared to the amount needed to reduce one or more symptoms of the autoimmune condition in a subject not receiving the sleep restorative agent." Corresponding amendments have been made to independent claims 25 and 40. Support for these amendments are found in the application as

filed at, *e.g.*, page 17, lines 10-15, page 19, lines 17-26; page 20, lines 29 and 30; and page 22, lines 3-6.

Further, Applicant notes that a *prima facie* case of obviousness under 35 U.S.C. § 103 requires, *inter alia*, a teaching or suggestion of all claim limitations in the cited reference, or references when combined.[38]

Here, the cited references do not teach or suggest all limitations of the claims as presently amended. In particular, and even assuming, for argument's sake only, a motivation to combine the cited references, there is no teaching or suggestion in these references of administering the therapeutic agent in an amount that is decreased relative to the amount needed to reduce a symptom of an autoimmune condition in a subject not receiving the sleep restorative agent. Wojtulewski teaches that rheumatoid arthritis causes insomnia[39] and that such insomnia can be treated with chlormezanone.[40] The cited references, however, do not teach or suggest any effect of a sleep restorative agent on rheumatoid arthritis itself, including any effect of a sleep restorative agent that reduces sympathetic tone on the efficacy of a therapeutic agent for rheumatoid arthritis. Thus, an "additive effect" of the two treatments would not be expected by the skilled artisan based on the cited art.

Indeed, Applicant's own disclosure shows that an additive or synergistic effect does not occur with certain treatments for insomnia.[41] In particular, in contrast to sleep restorative agents for treating sleep disturbance or restlessness (known surrogates for sympathetic tone), conventional sleep inducing agents did not increase efficacy of therapeutic agents[42] and, therefore, not all treatments for insomnia will work in sparing the effective amount of a therapeutic agent for treating autoimmune disease. This advantage of agents that reduce sympathetic tone, over other treatments for insomnia, would not have been expected or predicted

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[38] *See, e.g.*, MPEP §§ 2143 and 2143.03.
[39] *See* Wojtulewski *et al.* at page 456 (Introduction).
[40] *See id., passim.*
[41] *See* Specification at p. 27, l. 11, to p. 28, l. 19.
[42] *See id.* at p. 25, ll. 3-7; and p. 27, l. 11, to p. 28, l. 19.

by the skilled artisan on the basis of the cited art. This particular insight is provided only by Applicant's disclosure.

In view of the above, Applicant believes the present claims to be patentable under 35 U.S.C. § 103 over Lapin, Wojtulewski, and Lagos. Withdrawal of the rejection is respectfully requested.

Other Claim Amendments

New Claims 46 and 47

New claim 46 recites in independent form an embodiment of the method of claim 1 wherein the autoimmune disease is rheumatoid arthritis or Psoriatic arthritis, wherein the sleep restorative agent is pramipexole, lorazepam, clonazepam, gabapentin, ropinirole, and trazodone, and wherein the therapeutic agent is a steroid, methotrexate, soluble TNFα receptor, a NSAID, azathioprine, sulfasalazine, and hydrochloroquine. New claim 47 depends from claim 46 and specifies prednisone as the therapeutic agent.

Applicant notes that the Examiner has accepted treatment of rheumatoid arthritis and Psoriatic arthritis as enabled,[43] as well as the use of pramipexole, lorazepam, clonazepam, gabapentin, ropinirole, and trazodone[44] in the present methods. Further the Examiner appears to accept the working examples as evidencing enablement for the particular therapeutic agents used.[45] Accordingly, because steroids, methotrexate, soluble TNFα receptor, NSAIDs, azathioprine, sulfasalazine, and hydrochloroquine are exemplified for treatment of rheumatoid arthritis and Psoriatic arthritis, Applicant submits that claims 46 and 47 are enabled under 35 U.S.C. § 112, first paragraph. Applicant also believes these claims to be patentable for the cited art for reasons set forth above. For these reasons, Applicant believes new claims 46 and 47 to be allowable.

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[43] *See* Office Action dated May 20, 2005, at page 4.
[44] *See id.* at page 8.
[45] *See id.* at page 12, last paragraph, bridging to page 13.

New Claim 48

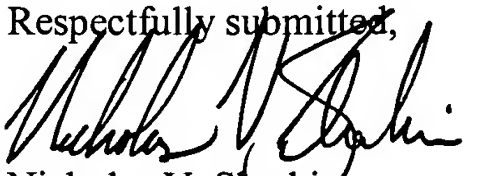
New claim 48 recites an embodiment of the present invention that includes the step of monitoring the subject for a decrease in sympathetic tone. Support for this amendment is found in the specification as filed at, *e.g.*, page 33, line 22, to page 34, line 14; and page 23, lines 20-26. Applicant believes this claim to be enabled by the specification for the reasons set forth above with respect to, *inter alia*, independent claim 1. Applicant further notes that none of the references cited under 35 U.S.C. § 103 teach or suggest the step of monitoring a subject for a decrease in sympathetic tone. Accordingly, Applicant also believes new claim 48 to be allowable under 35 U.S.C. § 103 for at least this reason, in addition to the reasons previously set forth.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



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